De Novo Design of Ubiquitin Substrate for Neuritic Plaque-Busting

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Background: Alzheimer's Disease pathogenesis is associated with the deposition of amyloid-beta (AB) protein aggregates in the brain. No treatment has been proposed to degrade pre-oligomeric AB peptides via the ubiquitin-proteasome pathway. The objective of this study is to design a ubiquitin substrate de novo which binds pre-oligomeric AB, thereby marking aberrantly folded peptides for degradation. Methods: Folding, packing, and docking algorithms were applied to a preliminary antiparallel beta-sheet backbone to fold the desired conformation. Monte Carlo sampling was applied during folding and packing to optimize backbone and side chain dihedral angles. The protein-protein docking protocol was driven by three processes: 1) initial perturbation, 2) low-resolution search, 3) high-resolution refinement. All models were evaluated against the Rosetta all-atom energy function. Results: Upon interface formation, favorable changes in Lennard-Jones energy, hydrogen bond energy, disulfide bond energy, and electrostatic energy were observed. The overall interaction energy for the native conformation (RMSD=0) is consistently negative, which indicates that protein binding is an energetically favorable process. Approximately 250 kJ/mole is released from interactions between the de novo protein and AB. Conclusion: The de novo ubiquitin substrate designed in this study has clinical potential in Alzheimer's Disease treatments. This study presents a proof of concept for protein design to facilitate ubiquitination of proteins associated with the pathology of other neurodegenerative diseases.

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